flow (CBF) because of its rapid degradation. To test if an intravenous ATP administration is timely degraded to adenosine at the heart, we measured CBF of the left anterior descending coronary artery and coronary arteriovenous differences of adenosine concentration (Ado) in the canine hearts. Infusions of ATP (5, 10, 20, and 40 μg/kg/min) into the systemic vein increased Ado from 7 ± 4 to 19 ± 7, 38 ± 7, 68 ± 11 and 112 ± 15 pmol/ml, although ATP, ADP and AMP concentrations in the coronary venous blood were not increased. An intravenous infusions of ATP increased CBF from 93 ± 5 to 127 ± 6, 149 ± 5, 168 ± 78 and 195 ± 6 ml/100 g/min, which was blunted by 8-sulfophenyltheophylline. Aortic pressure was decreased by 12 ± 5 mmHg from 107 ± 5 mmHg during 40 μg/kg/min of ATP infusion. During ischemia due to reduction of perfusion pressure by 56 ± 4%, an intravenous infusion of 40 μg/kg/min of ATP increased CBF (56 ± 3 to 66 ± 5 ml/100 g/min) with increased fractional shortening (9 ± 2 vs 14 ± 3) and lactate extraction ratio (−34 ± 5 vs. −17 ± 6%). We conclude that an intravenous administration of ATP can elevate myocardial adenosine levels, and improve myocardial contractile and metabolic function in the ischemic heart. Intravenous ATP administration may be promising for cardioprotection in the patients with acute ischemic heart diseases.

979-32 Endothelial-derived Relaxing Factor (Nitric Oxide) Has a Tonic Vasodilating Action on Coronary Collateral Vessels

Michael W. Frank, Kathleen R. Harris, KaLee A. Ahlin, Debra Quinn, Francis J. Klocke. *Feinberg Cardiovascular Research Institute, Northwestern U. Medical School, Chicago, IL*

Although coronary collateral vessels are known to react to several vasoactive agents, the role of endothelial-derived relaxing factor (EDRF) i unclear. Accordingly, the effects of N^{w}-nitro-L-arginine methyl ester (L-NAME), an agent blocking synthesis of nitric oxide, have been examined in six conscious chronically instrumented dogs. Coronary collaterals were induced in the left circumflex (LC) bed by either ameroid implantation or the repeated brief occlusion technique of Franklin. With the native LC artery occluded, LC pressure distal to the occlusion and flow in the LC bed were measured with a chronically implanted LC catheter and systemically administered microspheres before and after left atrial infusion of L-NAME (10 mg/kg):

	Control (Mean ± SEM)	L-NAME (Mean ± SEM)
Aortic Pressure (mmHg)	90 ± 4.1	113 ± 5.1*
LC Pressure (mmHg)	58 ± 6.6	47 ± 2.8
Aortic-LC Gradient (mmHg)	32 ± 3.3	66 ± 5.5*
LC Flow (ml/min/g)	1.41 ± 0.06	1.05 ± 0.18
Collateral Resistance (Aortic-LC Gradient/LC Flow)	23 ± 2.8	75 ± 15*

*$p \leq 0.01$, paired t

L-arginine, given following L-NAME, reduced the trans-collateral pressure gradient and resistance. We conclude that EDRF (nitric oxide) exerts a substantial tonic vasodilating effect in coronary collaterals. Disease-induced alterations in endothelial function may compromise collateral perfusion.

979-33 Ischemia-Reperfusion Injury Impairs Endothelium-Dependent Relaxations Acutely, but not Chronically, and does not Affect Endothelial Pertussis Toxin-Sensitive G Protein Function in Canine Coronary Arteries

John J. Lee, Leopoldo Olmos, Paul M. Vanhoutte [1]. *Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles, CA;* [1] *I.R.I.S., Paris, France*

While the acute endothelial dysfunction after ischemia-reperfusion injury (IRI) has been studied extensively, little is known about the chronic status of the reperfused coronary endothelium. Also, the effect of IRI on endothelial pertussis toxin-sensitive G protein function is unknown. Using heartworm-free mongrel dogs, percutaneous balloon catheters were used to occlude the left anterior descending coronary artery for 1 hr. The arteries were then reperfused slowly over 15–20 min to mimick the gradual reperfusion seen with thrombolytic therapy. This is in contrast to previous studies where reperfusion was sudden due to the use of clamps or snares to occlude the artery. After 1 hr (n = 6) or 4 weeks (n = 7) of reperfusion, the coronary arteries were dissected and suspended in organ chambers. Left circumflex coronary arteries, not exposed to IRI, from the same dogs were studied in parallel as controls. Endothelium-independent relaxations to the direct vascular smooth muscle dilators SIN-1 and lemakalim were unaffected by IRI. The endothelium-dependent relaxations to serotonin, thrombin, and ADP were significantly impaired 1 hr, but not 4 weeks, after IRI. The endothelium-dependent relaxation to serotonin was significantly inhibited by pertussis toxin (100 ng/ml). The endothelium-dependent relaxations to acetylcholine, bradykinin, and A23187 were unaffected by IRI either acutely or chronically. The endothelium-dependent relaxation to UK14304, which was nearly abolished by pertussis toxin, was not significantly impaired by IRI. These findings demonstrate that the early endothelial dysfunction after IRI is transient and not evident 4 weeks after reperfusion, and in contrast to the regenerated endothelium of porcine coronary arteries, the endothelial pertussis toxin-sensitive G protein function is not impaired by IRI.

979-34 Adriamycin May Impair Vascular Smooth Muscle Relaxation via a Nitric Oxide-Related Mechanism

Maurizio Cappelli-Bigazzi, Giuseppe Ambrosio, Carmine Battaglia, Antonello D'Andrea, Massimo Chiariello. *Division of Cardiology, University of Naples, Italy*

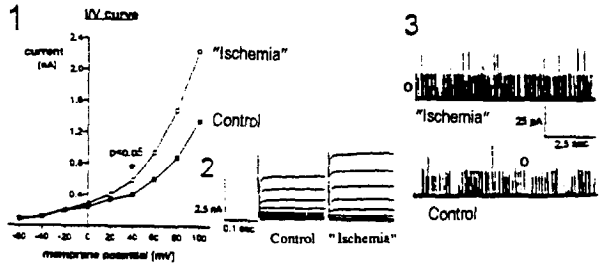
The free radical-dependent cardiac toxicity of adriamycin (ADR) is well known. Recently we observed that ADR is also able to affect vascular function, reducing endothelium-dependent relaxation. Moreover, endothelium-independent relaxation to nitroglycerin (NTG) was also impaired. Therefore, we wanted to investigate the mechanism through which ADR induces impairment of vascular smooth muscle function. In isolated rings of rabbit thoracic aorta preconstricted with 1 μM phenylephrine, maximal relaxation to NTG was decreased after 1 h incubation with ADR is a dose-dependent manner. In 6 experiments relaxation to NTG was 103 ± 3% in control rings, and was reduced to 97 ± 5% (p = NS), 85 ± 8 (p = NS) and 77 ± 8% ($p < 0.05$) in presence of 30 μM, 90 M and 150 μM ADR. As a consequence, ED_{50} increased from −7.93 ± 0.11 Log Mol NTG in controls to −7.81 ± 0.11 (p = NS), −7.20 ± 0.15 ($p < 0.05$) and −6.99 ± 0.25 Log Mol NTG ($p < 0.01$) with increasing concentrations of ADR. Similar results were observed with two other endothelium-independent vasodilators, SIN-1 (which activates guanylate cyclase) and isoproterenol (which activates adenylate cyclase). However, the inhibitory effect of ADR on NTG relaxation was much less pronounced if endothelium was absent. In fact, in denuded rings control maximal relaxation to NTG was 101 ± 3% and after 150 μM ADR it was 89 ± 4% (n = 6; P = NS), with no significant changes in ED_{50}. Furthermore, when nitric oxide synthesis in rings with endothelium was inhibited by 300 μM L-NAME, maximal relaxation to NTG was not significantly affected, being 100 ± 2% before and 85 ± 4% after 150 μM ADR incubation (n = 6; p = NS).

Thus, ADR may acutely impair smooth muscle relaxation. This impairment is dependent on the presence of normal endothelium. Formation of toxic peroxynitrite, via interaction of nitric oxide with ADR-formed free radicals, might mediate this phenomenon.

979-35 Factors of Acute Ischemia Increase Ca^{2+}-Activated K^+ Currents in Cultured Human Endothelial Cells

Jelin Pu, Johannes Wiecha, Johannes Waltenberger, Ulrike Mayr, Peter Weismüller, Matthias Kochs, Vinzenz Hombach. *Dept. of Cardiology, University of Ulm, Germany*

Ca^{2+}-activated K^+ channels (K_{Ca}) in endothelial cells and their response to some pharmacological agents are well known. However, the regulative function of these channels on transmembrane potential under ischemic conditions is still obscure. Therefore, we examine the effects of some ischemic factors on K_{Ca} channels in cultured human umbilical vein endothelial cells (HUVEC) by means of the patch-clamp technique. In whole-cell recordings (test potentials: −60 mV to +100 mV) the perfusion with an artificial ("ischemic") Tyrode solution (pH = 6.8; pO_2 = 45 mmHg, glucose-free) of HUVEC caused a significant increase of an outward current in the voltage range of +40 mV to +100 mV ($P < 0.05$; n = 15; Fig. 1: I/V-relationship, mean values; Fig. 2: sample of recordings). These currents were completely blocked by extracellular tetraethylammonium (TEA: 0.5 mM), whereas glibenclamide (10 μM) had no effect. In cell-attached patches (140 mM K^+ pipette solution) K_{Ca} channels were characterized by their typical voltage dependence, their block by TEA and a single-channel slope conduction of 215 pS (±5.17 pS; n = 10). Superfusion of HUVEC with the artificial solution caused a significant increase in the open-state probability NP_o (N: channels in the patch) of K_{Ca} channels from 0.0141 ± 0.0056 to 0.0377 ± 0.0119 at +80 mV ($p < 0.05$; n = 6) and 0.0645 ± 0.0221 to 0.1599 ± 0.0485 at +100 mV ($p < 0.05$; n = 7)(Fig. 3: sample of K_{Ca} recordings). Single channel conductance was not found to be changed. We conclude that the K_{Ca} channel in endothelial cells is



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influenced by basic ischemic factors and may, under pathophysiological conditions, be of importance in regulating Ca^{2+}-entry and stimulation-secretion coupling by modulating membrane potential.

979-36 Role of Endogenous Adenosine in Coronary Pressure-Flow Relationship in Dogs

Toshikazu Morioka [1], Masafumi Kitakaze, Tetsuo Minamino, Koichi Node, Yoshiro Shinozaki [2], Mitsuaki Chujo [2], Hidezo Mori [2], Jun Tanouchi [1], Masatsugu Hori [2], Takenobu Kamada. *The First Dept. of Med., Osaka Univ., Osaka, Japan; [1] Osaka Rosai Hospital Osaka, Japan; [2] Physiol. Dept., Tokai Univ., Isehara, Japan*

There have been conflicting evidence for the role of adenosine in coronary pressure flow relationship; although adenosine release increases when coronary perfusion pressure (CPP) is reduced, adenosine deaminase does not affect changes in coronary blood flow (CBF). To examine the role of endogenous adenosine in coronary pressure flow relationship, responses of CBF were observed during a stepwise reduction of CPP by 10 mmHg with and without 8-phenyltheophylline (8PT). In 32 dogs, the left anterior descending coronary artery was perfused from the carotid artery, where CBF was measured. According to the reduction of CPP, adenosine concentration detected in coronary venous blood was increased (CPP = 100 mmHg:7 ± 2, 80 mmHg:25 ± 3, 70 mmHg:53 ± 5, 40 mmHg:165 ± 11 pmol/ml). Administration of 8PT reduced CBF by 8 ± 3% at CPP = 100 – 70 mmHg, and by 34 ± 7% at CPP = 60 – 40 mmHg. When CPP was altered between 100 and 70 mmHg, 8PT markedly reduced ($p < 0.001$) fractional shortening (FS) and lactate extraction ratio (LER) (FS:9.8 ± 1.2 vs. 23.6 ± 1.2%, LER:–6.5 ± 1.9 vs. 26.7 ± 1.9% at CPP = 70 mmHg). Interestingly, 8PT markedly reduced End/Epi flow ratio by 35 ± 4% at CPP = 70 mmHg. Thus we conclude that when CPP is reduced, endogenous adenosine favors endocardial myocardial flow and preserves myocardial contractile and metabolic function.

979-37 Endothelin-1 at Pathophysiological Concentrations Induces Coronary Vasoconstriction via the ET-A Receptors

Charles R. Cannan, Roland R. Brandt, John C. Burnett Jr., Amir Lerman. *Mayo Clinic, Rochester, MN*

Endothelin-1 (ET-1) is an endothelial-derived coronary vasoconstrictor peptide which mediates its actions through the Endothelin-A and the Endothelin-B receptors. The current study was designed to test the hypothesis that at low-dose ET-1 to mimic pathophysiologic concentrations, ET-1 mediates coronary vasoconstriction through the ET-A receptor. Therefore, ET-1, (Group 1, n = 5), Sarafotoxin—a specific ET-B receptor agonist (Group 2, n = 5)—each at 2 ng/kg/min were infused into the left circumflex coronary artery in the anesthetized dog. In Group 3 (n = 5) the same dose of ET-1 was infused with 4 μg/kg/min of the specific ET-A receptor antagonist FR 139317. No difference in hemodynamics and coronary blood flow (CBF), coronary vascular resistance (CVR), and coronary artery diameter (CAD) were observed at baseline between the groups, and no alterations in systemic hemodynamics and plasma ET concentrations were observed during the protocol. CBF, CVR, and CAD were determined at baseline and during infusions and were calculated as % change (Δ) from baseline.

	Group 1	Group 2	Group 3
%ΔCBF	–48 ± 7*	–9 ± 3	–12 ± 3
%ΔCVR	105 ± 24*	24 ± 9	7 ± 6
%ΔCAD	4.6 ± 0.9*	–1.0 ± 0.3	–1.4 ± 0.7

Data are mean ± SEM, *$p < 0.01$ vs. Group 2 and Group 3. This study demonstrates in vivo that: ET-1 at pathophysiologic concentrations predominantly induces coronary vasoconstriction via the ET-A receptors at the level of the resistance vessels.

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Tuesday, March 21, 1995, 3:00 p.m.–5:00 p.m.
Ernest N. Morial Convention Center, Hall E
Presentation Hour: 4:00 p.m.–5:00 p.m.

980-38 A Randomized Study of the 8 French Hemostatic Puncture Closure Device vs Manual Compression After Coronary Interventions

Simonetta Blengino, Brenda Hann, Luigi Maiello, Shigeru Nakamura, Patrick Hall, Giancarlo Biagi, Leo Finci, Antonio Colombo. *Columbus Hospital, Milan, Italy*

The hemostatic puncture device (HPCD Kensey-Nash Co.) is a collagen plug system with an intraarterial anchor. To assess its efficacy, 56 patients were randomized after 8F percutaneous transcatheter interventions to either manual compression (MC) (25 patients) or HPCD (29 patients). There was no significant difference in the base line characteristics of age, gender, diabetes and hypertension between the two groups. Successful hemostasis was defined as the achievement of hemostasis without femoral hematoma, blood transfusion or vascular repair. Type of procedures, systolic blood pressure (BP), activating clotting time (ACT), total hemostasis duration, time to mobilization and hospital stay after the removal of the sheath were compared. Ultrasound vessel measurements made at the puncture site after the procedure and 2 months follow up (F/U) were also compared.

	MC (n = 25)	HPCD (n = 29)	p Value
Successful hemostasis	24 (96%)	26 (90%)	0.71
Stent implantation	20 (80%)	27 (93%)	0.30
Systolic BP (mmHg)	129 ± 9	134 ± 18	0.34
ACT (seconds)	163 ± 17	274 ± 61	0.0001
Hemostasis time (minutes)	16 ± 5	2 ± 6	0.0001
Time to mobilization (hr)	18.1 ± 3.6	15.8 ± 3.3	0.018
Hospital stay (day)	1.2 ± 0.4	1.1 ± 0.4	0.22
Vessel diameter (mm)	7.9 ± 1.6	7.9 ± 2.2	0.93
Vessel at F/U (mm)	7.6 ± 1.0	7.7 ± 1.1	0.69

There was 1 unsuccessful hemostasis due to hematoma in the MC and 2 in the HPCD group. There was one rebleeding episode requiring prolonged manual pressure in the HPCD group. All stent patients were treated without subsequent anticoagulation. The device anchor in the vessel was small enough that it did not reduce the vessel diameter by ultrasound. This result was confirmed also at 2 month ultrasound follow up. *Conclusions.* (1) The HPCD provides rapid hemostasis despite a high ACT. (2) HPCD enables prompt sheath removal despite effective anticoagulation and also reduces the effort of manual compression. (3) HPCD use allows for a reduction in mobilization time and short hospital stay.

980-83 Advantages of Sealing Arterial Puncture Sites After PTCA with a Single Collagen Plug: A Randomized, Prospective Trial

Sigmund Silber, Aina Björvik, Andreas Rösch, Holger Mühling. *Dr. Müller Hospital, Munich, Germany*

Only little data exist comparing collagen plugging of arterial puncture sites at identical conditions with conventional sheath pulling. Furthermore it has not been investigated whether one single plug is also effective after PTCA. Therefore we randomized 150 pats to either one single collagen plug or conventional sheath (8F) pulling. Both groups did not differ in age, gender, BSA, BP or APTT.

Results:

	single collagen plug	control
Compression time (min)	3 ± 3	16 ± 7*
normal local findings	87%	77%
little local swelling	8%	21%*
severe local swelling	5%	2%
hematoma ≤ 7 cm	20%	29%
hematoma > 7 cm	5%	4%
patient comfort index	8.3	3.5*

*$p < 0.05$

Conclusions: Collagen plugging of arterial puncture sites after PTCA is as effective as conventional sheath pulling and significantly reduces time to hemostasis. Patient comfort is markedly increased. Since one single plug is very effective, costs may be cut in half.

980-84 Restenosis of Stented Dialysis Conduits Caused by Stent Collapse, not Neointimal Proliferation

Kenneth Rosenfield, Robert Schainfeld, Waqar Kahn, Ann Pieczek, Emer Grall, Sean McGarr, Jeffrey M. Isner. *St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA*

Restenosis at stented sites has been attributed to neointimal proliferation. Stent collapse from external compression may also contribute to restenosis (Resten). We performed PTA and stenting in 6 hemodialysis conduits in five patients. Four subclavian and two brachiocephalic vein stenoses were initially treated with PTA and Palmaz stents. All sites developed early restenosis (mean time = 3.3 ± 2 months). Whereas angiography suggested a classic proliferative mechanism of restenosis, intravascular ultrasound (IVUS) demonstrated eccentric stent collapse: stent configuration was ovoid or slit-like, rather than circular, and struts were not apposed to the vessel wall, but instead were protruding into the lumen directly abutting the IVUS probe. Neointimal proliferation was absent in all cases. Redilation was performed in all cases, with additional stents placed in the 4 subclavian veins. All 6 vessels